12. The Toxic Atheroma

"Fragmentation and embolization of platelet-rich mural thrombi at the site of vessel injury could cause damage by obstructing myocardial microcirculation."
JF Mustard, [128]

The Fundamental Acute Lesion

All acute coronary syndromes (ACS) can be traced, in one way or another, to UPs and the resulting sequelae [57,148]. The UP, therefore, is the fundamental lesion underlying the development of ACD and is the initial precipitating event leading to these syndromes [57]. The many different ACSs that develop as a result of PU are due to the many interacting factors triggered by this breach in endothelial integrity, including the size, location, number, and specific types of PU [57,148,154,198,199].

The primary aim of this chapter is to make clinical-pathologic correlations in support of our hypothesis that the initial symptoms and signs associated with the onset of many ACSs are caused by the discharge of plaque contents, particularly plaque toxins from UPs, NOT by ischemia. Plaque contents include any chemical agents, particulate matter, or tissue fragment microemboli discharged from UPs. A secondary aim, in Chapter 13, is to discuss the potential role of plaque toxins in the subsequent manifestations of the different ACSs.

The Toxic Atheroma

Necrotic tissue stimulates bodily responses to remove it because it contains chemical agents that trigger inflammatory mediators, injuring surrounding viable tissue [18]. Necrotic tissue becomes increasingly acidotic as cells undergo degeneration and destruction, and as cellular proteins are denatured [200]. A necrotic focus will spontaneously ulcerate and drain the necrotic material into a body cavity, onto the body surface, or be resorbed and undergo fibrotic replacement.

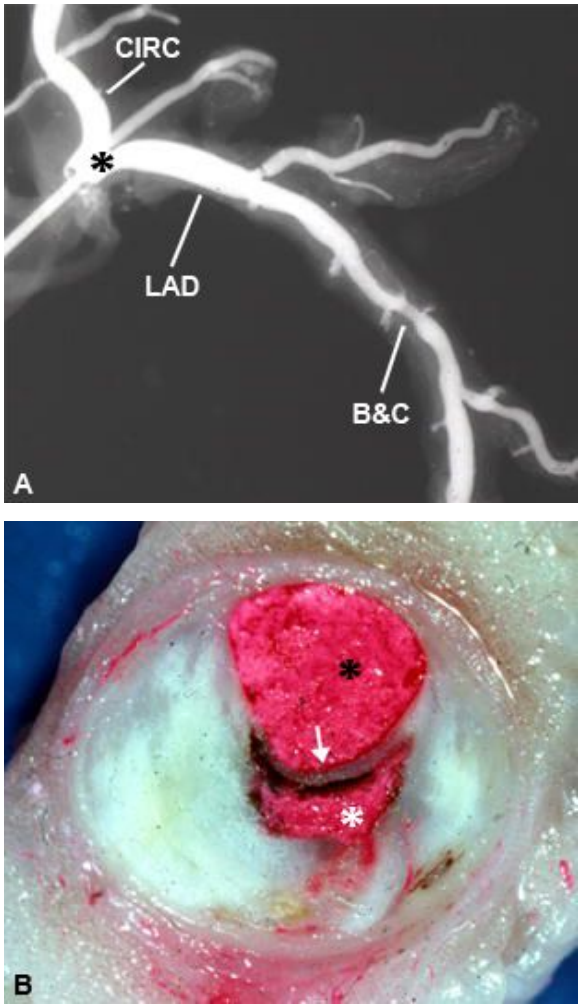
Some of the chemical toxins associated with atheromas are products of lipid metabolism [61], acids generated as part of cell necrosis [200], inflammatory cytokines [18], immune complexes [201], and other unknown factors. Oxidized LDL, one of the most well known IAs, is believed to play a major role in the formation of the necrotic core [61]. Reactive oxygen species are known to be highly toxic metabolites, causing immediate injury to cells, but the source of these free radicals has not been fully determined [202]. Atheromas contain reactive oxygen species and may serve as a source of these toxic metabolites at the time of PU [203–205]. Based on our observations of resorption and possible reversal of vascular calcification (Chapter 5), the necrotic core may also contain products of bone metabolism, such as HA, a particularly irritating compound [96]. HA may produce similar effects when discharged directly into the coronary circulation. Atherosclerosis is the only disease where necrotic material and all associated chemical toxins, are consistently discharged directly into the coronary circulation, the most important blood supply in the body.

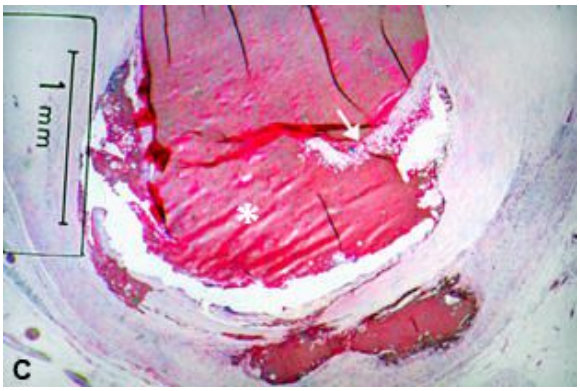
How toxic are the contents of an atheromatous core? Our reference to "plaque toxins" in this chapter is meant to include any and all non-physiologic chemical agents, present in the necrotic core, that could produce direct stimulation and/or injury to cardiac tissues when released into the coronary circulation. Lyford and Connor, et al. [206], using extracts made from human atheromas, injected the extracts intravenously into 10 rats. Six of the 10

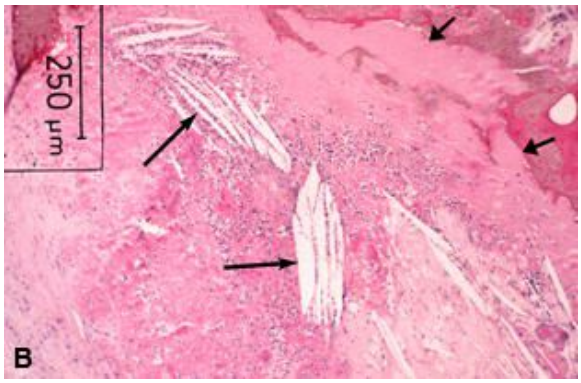
died of cardiac causes within minutes of the injection. These sudden cardiac deaths were believed to be due to direct, toxic effects of the chemical agents contained in these extracts on the heart [Connor, personal communication]. Nine of these rats also showed pulmonary emboli, indicating these toxins and/or plaque contents are quite thrombogenic [198]. The possibility that chemical agents contained within the necrotic core are potent cellular toxins that could cause sudden and immediate direct injury to cardiac tissues when released into the coronary circulation must be considered in the pathogenesis of ACD [207].

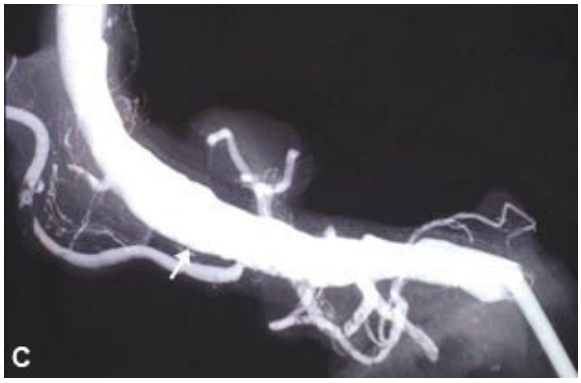
The quantity of plaque toxins and other necrotic material discharged at the time of PU will depend on the anatomic features associated with each plaque, the location of the plaque within the coronary tree, the size of the plaque, and the size of the PU [57]. No two PUs are identical. Figures 8, 17–20, 22, 24, and 26, illustrate various types of PUs, ranging from tiny shoulder ulcerations to completely shelled-out plaques. The amount of plaque contents, and, therefore, the amount of plaque toxins released at the time of PU may be expected to vary widely from plaque to plaque. We assume the effects of these plaque toxins will depend upon the concentration, dose, the speed of release, the duration of the discharge, the inherent toxicity of the agents, and how quickly these agents can be neutralized and removed. Consideration must also be given to the number and age of the UPs in any given patient because multiple, chronic UPs are the rule in patients with acute coronary disease [57,148,150,156,208,209].

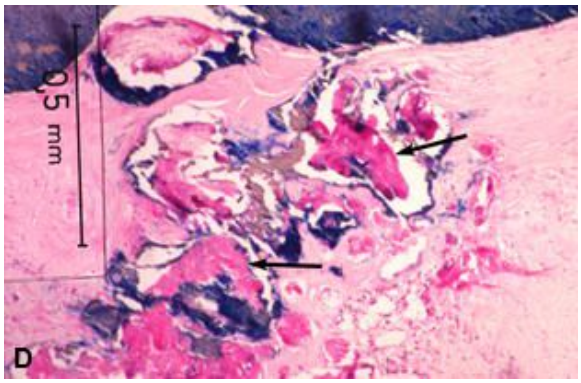
For example, a small amount of toxin discharged intermittently from a tiny shoulder ulceration (Figure 8) may produce no clinical symptoms, whereas a large bolus of toxin from a shelled-out plaque (Figures 18, 24), may precipitate a sudden, acute coronary event. Furthermore, the sudden and spontaneous discharge of these toxins at the time of PU may be expected to produce immediate symptoms and injury when the toxins circulate to downstream structures [202]. The effect of these plaque toxins discharging directly into the coronary circulation may be similar to infusing absolute alcohol directly into the first septal branch of the LAD to produce a focal, controlled, myocardial infarction in the treatment of hypertrophic cardiomyopathy [210,211].











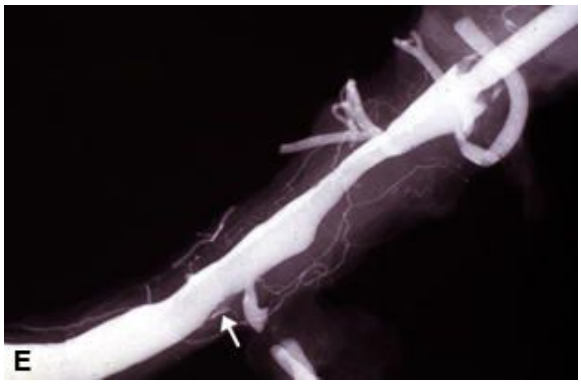
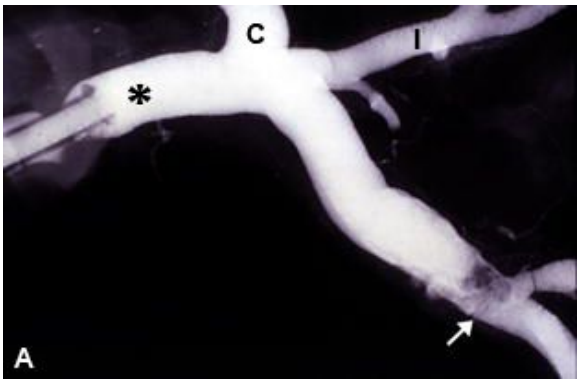


Figure 24: Pathologic lesions of a 39-year-old white male who died SCD outside the hospital. **A**, Dissected coronary artery showing moderate stenosis in the mid-LAD branch. Asterisk = main left coronary artery. **B**, Gross view of the narrowing in **A** showing 80% luminal stenosis with an intact fibrous cap (white arrow) overlying an empty, shelled out, necrotic core (white asterisk). No occlusive thrombus is present. Black asterisk = normal lumen. **C**, Histologic section of the UP in **B**, showing a remnant of the fibrous cap (white arrow) and an empty necrotic core (white asterisk) without evidence of thrombosis. **D**, Cholesterol crystals and other plaque debris in a small branch of the vasa vasorum supplying the artery wall distal to the UP in **B**.



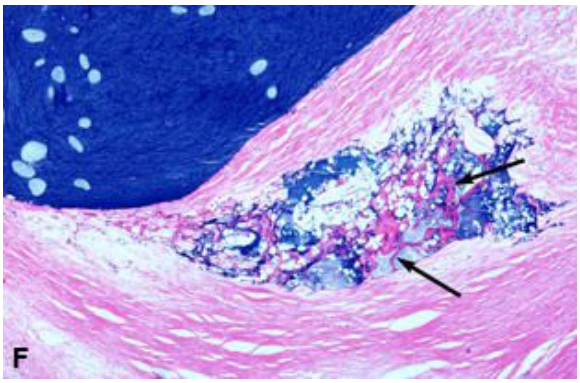
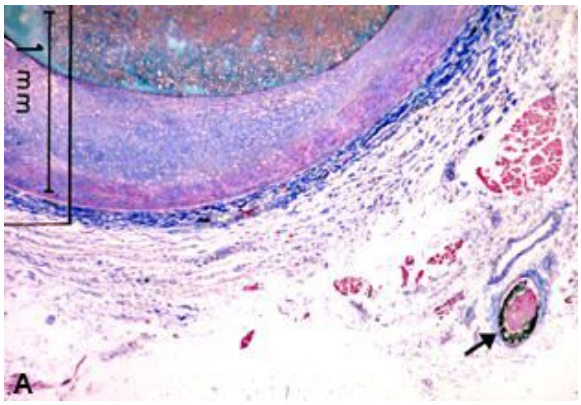


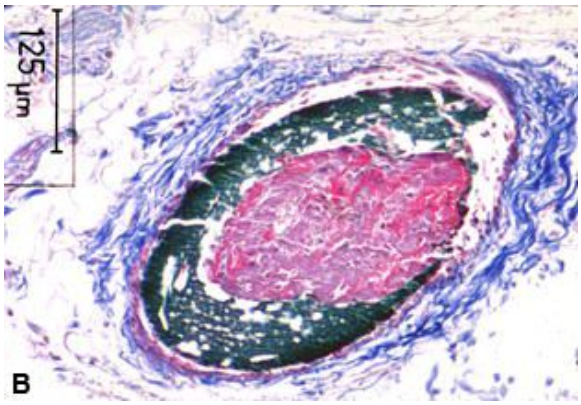
Figure 26: **A**, X-ray of proximal left coronary artery in a 38-year-old male who died SCD outside the hospital. Asterisk = Left main coronary artery. White arrow = Acute thrombotic obstruction of the LAD coronary artery proximal to a bifurcation. C = CIRC artery. I = Intermedius branch. **B**, Microscopic view of the thrombus in **A** showing plaque contents and cholesterol crystals (long black arrows) mixed with thrombus (short black arrows). **C**, X-ray of proximal RCA in an 86-year-old female who died of myocardial rupture several hours after receiving streptokinase for acute anterior myocardial infarction. White arrow = Site of intraintimal thrombus. **D**, Microscopic view of intraintimal thrombus shown in **C**. Black arrows identify thrombus mixed with blue injection mass indicating thrombus formed within a non-obstructing UP. **E**, X-ray of proximal RCA of 37-year-old male who died SCD outside the hospital. White arrow = Site of UP with intraintimal thrombus shown in **F**. **F**, Note injection mass has replaced plaque contents and fibrin strands have formed (black arrows). **B**, **D** & **E** all H & E stain.

Embolization of Plaque Tissue

Embolic particulate matter, tissue fragments, and platelet microemboli from UPs are found in the majority of patients who died of ACD [64,128,212–216]. The effect of this embolic material will depend upon such factors as consistency, number, size, the speed with which they are released, the speed with which they are removed, and the specific cardiac structures affected. Figure 23 shows several examples of embolic material in the lumen of the epicardial arteries, the vasa vasorum, the myocardial arterioles, and in the nutrient arteries to the conduction system of different patients. All emboli shown in Figures 23–25 were located distal to UPs in the epicardial arteries and passed to the distal microcirculation. If embolic material circulates to these structures, then so do any associated plaque toxins.

If the embolic plaque tissue is friable, as might be expected of necrotic tissue (Figures 6,8), and undergoes easy dispersion, the obstruction to flow in the microcirculation may be insignificant. Large tissue fragments (Figure 6F), may be more serious because such fragments will not be easily dispersed and could cause prolonged obstruction of relatively large arteriolar branches. The result may be the production of focal ischemia or even infarction of the myocardium [64,128,212,214]. Obstruction of the microcirculation by embolic plaque material, even transient obstruction, may delay the dilution, neutralization, or washout of any associated plaque toxins, resulting in greater toxic injury.





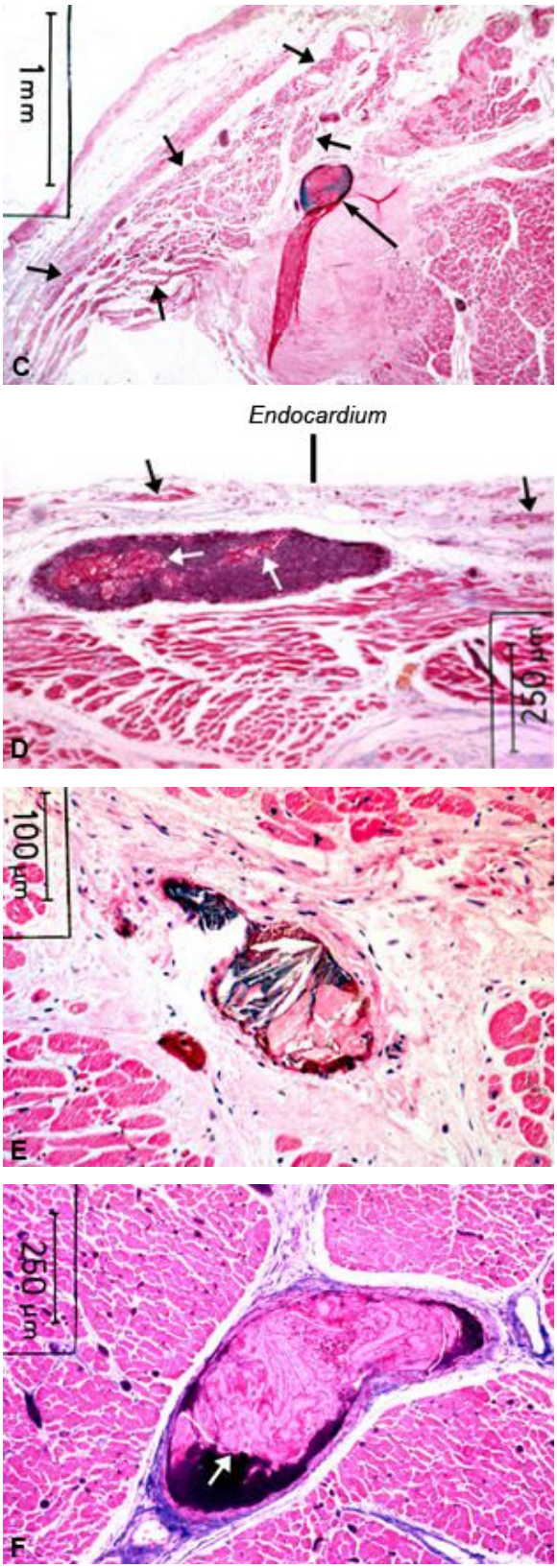
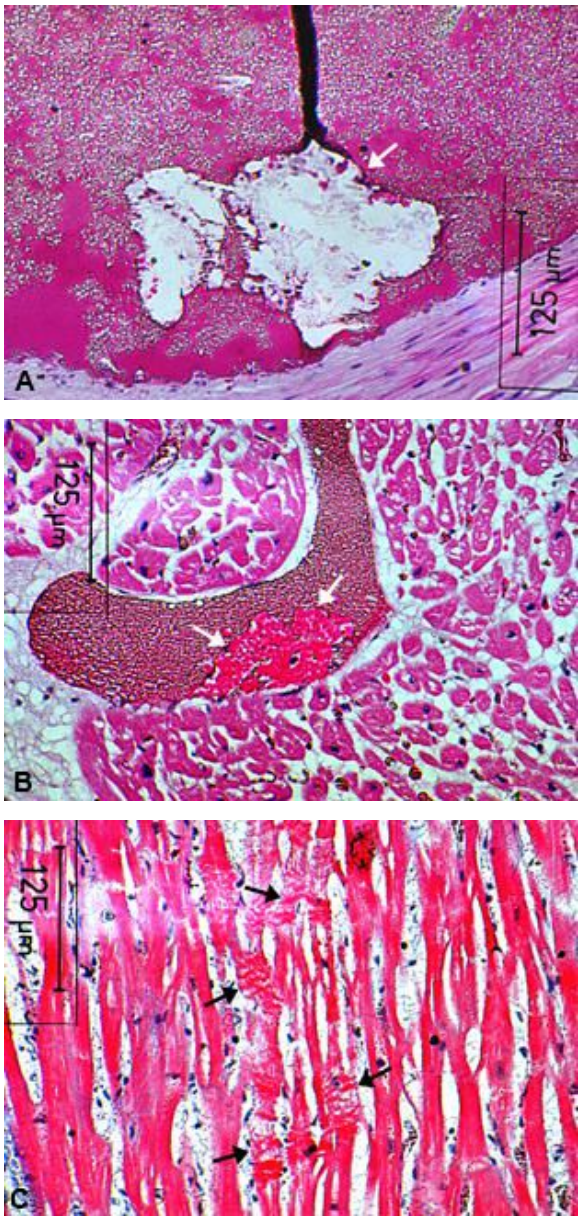


Figure 23: **A**, Low-power and **B**, high-power view of microembolus in the vasa vasorum (arrow) in the mid-CIRC artery of a 39-year-old white male who received streptokinase to relieve thrombotic occlusion causing acute inferior myocardial infarction. **C**, Microembolus in an arteriole (long arrow) lying adjacent to the proximal left bundle branch (short arrows). **D**, Small myocardial arteriole, adjacent to left ventricular endocardium and distal left bundle branch (black arrows), containing a small microembolus (white arrows). **E**, Embolic plaque contents in the upper interventricular septum of an 82-year-old white female who died of cardiogenic shock in the hospital. **F**, Large intramyocardial microembolus (white arrow) of a 34-year-old white male with a history of chest pains who died SCD outside the hospital. This microembolus was distal to a non-occlusive thrombus in the LAD artery.



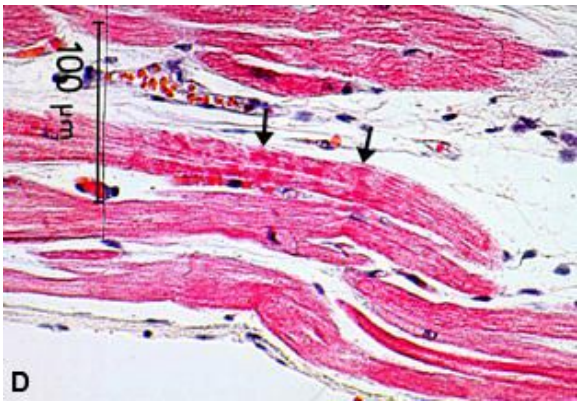


Figure 25: The photographs shown here are from the same patient in Figure 24 and distal to the UP in Fig. 24B. **A**, Plaque contents and debris (white arrow) in the LAD distal to the UP. **B**, Small microembolus (arrows) in a myocardial arteriole. **C**, Section of the myocardium showing contraction bands (arrows). **D**, Section showing contraction bands (black arrows) in the left bundle branch.

Initial Symptoms

By "initial symptoms" we mean those symptoms and signs occurring within minutes after the onset of an ACS. If initial symptoms of ACD are caused by direct stimulation and/or injury of cardiac tissues by plaque toxins discharged from UPs, and the effects are immediate [202], then the initial symptoms should coincide with the moment of PU or the moment the toxins are released.

The onset of symptoms should mark the moment when plaque toxins reach the myocardium or other structures. The initial symptoms, then, could reflect toxic stimulation or injury, rather than ischemic injury. Time is required for ischemic injury to develop and for ischemic metabolites to form [217]. Ischemic metabolites would not be present in sufficient amounts to cause immediate stimulation or injury of cardiac structures in the first few minutes after the onset of symptoms, even when coronary flow is acutely reduced [218,219]. We postulate the initial symptoms associated with ACSs are due to toxic rather than ischemic injury.

Downstream Structures

If the initial symptoms of ACD are caused primarily by the discharge of plaque toxins, we should see histological evidence consistent with such toxic injury by examining downstream structures. The first tissue to be potentially affected by plaque toxins is the endothelium of the artery containing the UP and the endothelium of the microcirculation fed by that artery. Recent studies show microparticles of endothelial origin are present in the circulating blood of patients with ACD, indicating endothelial injury somewhere in the vascular system [220]. We have observed extensive, circumferential, endothelial erosions extending over a distance of several cm (Figure 17D and E), consistent with injury by an erosive toxin. Such erosions, localized to one coronary artery and distal to an UP, provide evidence the endothelium and the subendothelial tissue have been injured by local substances, presumably originating from the UP. If the offending agent causing this erosion were a circulating systemic toxin, then we would expect all arteries, not selected arteries, to show similar erosions.

Endothelial injury by plaque toxins from UPs has implications for the pathogenesis of new atherosclerotic lesions because any endothelial injury may provide a point of entry for the IA [1]. Endothelial injury produced by plaque toxins may be important in the pathogenesis of multiple, separate plaques in a single coronary artery (Figures 1 and 2), producing multicentric lesions (Chapters 1 and 5). Further, these injurious chemical agents may injure and weaken the fibrous cap of a distal plaque (Figures 17B,C, and F) and may contrib ute to the formation of a second UP within the same coronary artery. We have found as many as 3 or more widely separate UPs within the same coronary artery in 13 of 83 (16%) patients who died of ACD [57].

In addition, the circulation of large amounts of potent toxins to the distal myocardial microcirculation may severely injure or destroy the capillary endothelium and thus obstruct blood flow through the affected area, even with adequate antegrade flow. This mechanism may be one explanation for the no-reflow phenomena observed in some ACSs [221,222], discussed in Chapter 13 in the section on acute myocardial infarction (AMI). The release of plaque toxins from UPs may affect other cardiac structures, including the SMC and nerves of the media and adventitia of the epicardial artery, the conduction system, and the cardiac chemoreceptors.

The artery wall overlying an atherosclerotic plaque often has a highly developed vasa vasorum [223] that could carry any circulating plaque toxins quickly to the adventitia. Injury and/or stimulation of the media and/or adventitial nerves by plaque toxins could potentially produce vasoconstriction of a focal portion of the coronary artery, as well as chest pain, by stimulating sympathetic nerves.

If the artery containing an UP supplies a portion of the conduction system, these toxins may cause direct injury or dysfunction of the pacemakers and/or the peripheral conduction system, leading to various arrhythmias in the absence of ischemia [218,224].

Plaque toxins may also stimulate the cardiac chemoreceptors, activating reflexes such as the Von Bezold Jarish (VBJ) reflex [225], producing the bradycardia and hypotension often observed when this reflex is activated during acute coronary events. By definition, the VBJ reflex is produced by chemical stimulation of the cardiac chemoreceptors located throughout the heart, further implicating a chemical agent in the pathogenesis of the initial symptoms.

In Review

Considerable histologic and clinical evidence exists that plaque toxins, originating from UPs, have the potential to produce the initial symptoms by stimulating or injuring many cardiac structures. These toxins may play an important role, in both the initial clinical and subsequent manifestations as well as the prognosis of various ACSs.